REMARKS:

Claims 1, 2, 3 and 5 have been amended to state that the recombinant particle is a vaccine. Claims 13, 14, 15, 17, 19 and 20 have been amended to state that the recombinant particle is used in a method of vaccination.

Support for this amendment may be found at least at page 11, line 5 to page 12, line 13, page 15 line 21 to page 16, line 22 and Tables 3-6 and 8.

Claims 1-3, 5, 13-15, 17, 19-23, 25 and 27-31 were rejected under 35 USC 103(a) as unpatentable over Ito in view of Kahn.

Applicant respectfully notes that the previous office action states that 'Ito does not teach a method of eliciting an immune response or preparing a pharmaceutical composition'.

The office action further states that 'Ito teaches a recombinant VSV particle wherein the Ebola virus glycoprotein was incorporated into recombinant VSV particles Kahn teaches a recombinant VSV expressing foreign protein wherein the RSV G replaced the VSV G (glycoprotein) in the viral genome. This combination of references teaches the instant claimed invention'.

Applicant respectfully disagrees. Specifically, applicant notes that Kahn teaches that in order to recover the VSVΔG-RSV G and VSVΔG-RSV F particles, they must be propagated on a modified BHK cell line which expresses VSV G (Kahn, page 11081, 2nd column, 1st complete paragraph). Thus, the particles taught by Kahn contain VSV G in addition to RSV F or RSV G. As discussed previously, the presence of the VSV G in the particle limits the utility of the system as if an immune response is elicited by the particle, there will also be immunity against VSV G, meaning that the system can only be used as a single use. Furthermore, the particle taught by Kahn does not meet the limitation in the instant claims that only the VHF glycoprotein is expressed on the surface of the particle.

Yet further, Kahn in fact discovered that VSVΔG-RSV G did not induce an immune response or protective immunity although VSVΔG-RSV F did. Specifically, Kahn states:

'VSVΔG-RSV G and VSVΔG-RSV F failed to induce serum RSV neutralizing titers as determined by the plaque reduction assay' (page 11083, column 1, 2nd complete paragraph)

'VSVΔG-RSV F, but not VSVΔG-RSV G, induced an RSV-specific antibody response (Fig. 4B). These results were in contrast to the neutralizing antibody titer results (Table 1), in which serum from mice immunized with VSVΔG-RSV F recombinants expressing RSV proteins failed to neutralize RSV.' (Kahn, page 11083, paragraph spanning columns 1 and 2).

'RSV replicated to significant titers in mice which were previously immunized with either wild-type VSV or VSVΔG (Fig. 5)... RSV was not detected in either BAL fluid or lung tissue from any mouse immunized with VSV-RSV G, VSV-RSV F, or VSVΔG-RSV F. VSVΔG-RSV G failed to protect from RSV replication.' (Kahn, page 11083, 1st complete paragraph).

Thus, Kahn teaches that VSVΔG-RSV G cannot elicit a protective immune response but that VSV-RSV G can. It is further of note that as discussed above even the VSVΔG-RSV G contains VSV G supplied in trans. As discussed above, this is not applicant's invention.

The office action further states that 'the person of ordinary skill in the art would have been motivated to make use of a VSVΔG to elicit an immune response because Ito teaches it is effective with Ebola (VHF), and reasonably would have expected success because of the teachings of Kahn'.

Applicant again respectfully disagrees. As discussed above, when Kahn used VSVΔG constructs, VSV G was supplied in trans and one of the two constructs

failed to elicit an immune response. Accordingly, combining Kahn and Ito, one of skill in the art might conclude that a VSVΔG - VHF glycoprotein construct could be made and if VSV G was provided in trans, such a particle might elicit an immune response. However, these particles, which contain VSV G and a VHF glycoprotein are not applicant's invention, for reasons described above. Furthermore, one of skill in the art would on considering Kahn in its entirety remember that the VSVΔG-RSV F did not produce neutralizing antibodies and would accordingly conclude that even supplying VSV G in trans may not provide a protective immune response and based on Kahn would not produce neutralizing antibodies and decide that a VSV – VHF construct was far more likely to be successful as a vaccine despite the limitations thereof as discussed above.

Regarding Ito, this reference showed that Ebola GP could confer infectivity if supplied in trans. However, infectivity alone does not guarantee propagation and propagation does not guarantee an immune response let alone vaccination. Furthermore, it is unclear how Ito and Kahn are to be combined to produce applicant's invention without the application of hindsight. Specifically, is the Ebola GP substituted for the VSV G supplied in trans, given that Ito showed Ebola GP will confer infectivity or is the Ebola GP substituted into the VSVΔG construct for the RSV F (which did not elicit neutralizing antibodies) or for the RSV G (which did not elicit an immune response at all) with VSV G continuing to be supplied in trans? That is, is the infectivity property of Ebola GP to substitute for VSV G taught by Ito being used to substitute Ebola GP for the VSV G being supplied in trans or is Ito teaching that Ebola GP is a protein of interest and should be substituted for RSV G with VSV G continuing to be supplied in trans? Furthermore, it is unclear what incentive or motivation there would be to substitute the Ebola GP for RSV G in the VSVΔG construct without supplying VSV G in trans, given that even when Kahn supplied VSV

G in trans, this construct did not elicit an immune response. Alternatively, one can argue that the combination of Ito and Kahn teaches a system which could be used to determine the important residues for RSV F-based fusion.

As noted above, the office action states that 'Ito teaches a recombinant VSV particle wherein the Ebola virus glycoprotein was incorporated into recombinant VSV particles Kahn teaches a recombinant VSV expressing foreign protein wherein the RSV G replaced the VSV G (glycoprotein) in the viral genome. This combination of references teaches the instant claimed invention'.

Applicant notes that as discussed above Kahn teaches a recombinant VSV expressing foreign protein wherein the RSV G replaced the VSV G in the viral genome and VSV G was supplied in trans and that particle did not elicit an immune response. Combining Ito as suggested by the examiner to substitute Ebola GP for RSV G would still require that VSV G be supplied in trans and even with VSV G being supplied in trans, Kahn teaches that when RSV G was used in the VSV ΔG constructs even with VSV G being supplied in trans, no immune response was obtained. Thus, combining Ito and Kahn as taught by the examiner would provide a recombinant particle which the foreign glycoprotein (VHF glycoprotein such as Ebola GP) has replaced the native VSV glycoprotein. However, because Kahn teaches that VSV G must be supplied in trans, the VHF glycoprotein would not be the only glycoprotein expressed on the surface of the recombinant VSV particle as the VSV G provided in trans would also be present. As discussed above, this limits the utility of the system, meaning that the VSV 'vehicle' can only be used once with a given patient due to host immune reactions to VSV G. Furthermore, based on the results obtained by Kahn, one would expect that even with supplying the VSV G in trans, no immune response or no neutralizing antibodies ay be obtained and it would be better to use native or wild-type VSV constructs. Thus, Kahn teaches that supplying VSV G is important for

getting an immune response and that wild type levels of VSV G provided better results than supplying VSV G in trans which in one case produced no immune response and in the other case produced no neutralizing antibodies. Accordingly, there is no teaching in Kahn that VSV G can be omitted entirely from the particles.

Applicant's invention is a vaccine comprising a recombinant vesicular stomatitis virus (VSV) particle comprising a nucleic acid molecule encoding a viral hemorrhagic fever (VHF) glycoprotein inserted into the viral genome wherein the foreign glycoprotein has replaced the native VSV glycoprotein and only the VHF glycoprotein is expressed on the surface of the recombinant VSV particle, wherein said recombinant VSV particle is infectious.

Thus, the inventors have discovered that a recombinant VSV particle having only a VHF glycoprotein on its surface with no VSV G protein can be used as a safe and effective vaccine. As discussed above, this is not taught or suggested by the prior art. As discussed above, Kahn showed that VSVΔG-RSV G with VSV G supplied in trans did not elicit an immune response and VSVΔG-RSV F with VSV G supplied in trans did not elicit neutralizing antibodies. As such, Kahn teaches that VSVΔG constructs even with VSV G supplied in trans do not elicit neutralizing antibodies (RSV F) or any immune response at all (RSV G). Combining Ito which showed that Ebola GP could be used to confer infectivity to VSVΔG constructs with Kahn possibly suggests that Ebola GP could be substituted for VSV G and supplied in trans. However, as discussed in the previous response, there were considerable reasons for concern based on earlier literature regarding what properties an infectious particle expressing a VHF glycoprotein would have as at least one VHF glycoprotein was believed to cause or contribute to the symptoms associated with VHF diseases. As such, there was no guarantee that such a construct could be used safely or given the results obtained by Kahn that such a construct would elicit the desired protection even

if VSV G was supplied in trans, let alone in a particle that had only a VHF glycoprotein and no VSV G.

In summary, the inventors have discovered that a VSVΔG particle can be constructed which has only a VHF glycoprotein and no VSV glycoprotein that can be used safely as a vaccine based on its ability to propagate. This is in contrast with the prior art which teaches that VSV G must be supplied in trans and even then an immune response may not be elicited (Kahn) and that a propagating virus expressing one VHF glycoprotein (Zaire strain of Ebola) can cause symptoms associated with VHF and accordingly may not be safe. Ito teaches that Ebola GP can confer infectivity to a VSVΔG particle but as discussed above infectivity does not guarantee propagation, propagation does not guarantee an immune response and an immune response does not guarantee vaccination. Accordingly, the prior art taught that a VSVΔG-VHF G construct may not elicit an immune response even if VSV G was supplied in trans but such a construct could have considerable side effects. The inventors found surprisingly that neither was the case and that a safe and effective vaccine could be developed.

In view of the foregoing, further and more favorable consideration is respectfully requested.

Respectfully submitted
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